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EXAMINER	
KERR, KATHLEEN M	

ART UNIT	PAPER NUMBER
1652	14

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/720,840	LEADLAY ET AL.	
	Examiner	Art Unit	
	Kathleen M Kerr	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-30 and 38-43* is/are pending in the application.

4a) Of the above claim(s) *41 and 42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-30,38-40 and 43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Application Status

1. In response to the previous Office action, a non-Final rejection (Paper No. 10, mailed on May 3, 2002), Applicants filed an amendment and response received on November 13, 2002 (Paper No. 11) and a supplemental amendment on February 10, 2003 (Paper No. 13). Said amendments cancelled Claims 31-37, amended Claims 16-20, 22, 26 (twice), 28-30, and 38-39 and added new Claims 41-43. Thus, Claims 16-30 and 38-43 are pending in the instant Office action.

Election

2. Originally examined were claims 17-30 and 38-40 drawn to type I polyketide synthases wherein at least a part of the extension module is not naturally associated with (are heterologous to) the loading module. Claim 16 was inadvertently omitted from examination in the previous Office action as it belongs with the elected group since its language implies type I PKS enzyme systems.

Claims 41-42 are withdrawn from further consideration as non-elected inventions. Claims 16-30, 38-40, and 43 will be examined herein.

Priority

3. As previously noted, the instant application is granted the benefit of priority for International Application No. PCT/GB99/02044 filed on June 29, 1999 and UK Application No. 9814066.4 filed on June 29, 1998.

Drawings

4. The drawings are considered informal for the reasons detailed in the previously attached copy of PTO Form 948 (see Paper No. 10). Appropriate correction is required in response to the instant Office action and may not be held in abeyance (see 37 C.F.R. § 1.85(a)).

Compliance with the Sequence Rules

5. In response to the previous request to comply with the sequence rules, Applicants have amended the specification to comply except where noted below. In view of these exceptions, the instant application still fails to **fully** comply with the requirements of 37 C.F.R. § 1.821 through 1.825; Applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990).

a) In Figures 2A-2D, 20 polypeptide sequences are disclosed without benefit of SEQ ID NOs. In response to the previous Office action, Applicants note that the SEQ ID NOs will be added to the Figure; however, such an amendment to the figure requires Examiner approval (not just Draftsman approval) as implied in Applicants' remarks. Appropriate amendments to the drawings are by way of filing substitute sheets with changes sketched in red ink and filing instructions to replace the originally filed drawings with the amended sheets (see M.P.E.P. § 608.02(p)).

b) In Figures 4A-4C, 5 polypeptide sequences are disclosed without benefit of SEQ ID NOs. See note above about amendments to the drawings.

c) In Figure 7, DNA sequences are disclosed without benefit of SEQ ID NOs. See note above about amendments to the drawings.

Appropriate amendment to the drawings (or to the description of the drawings) is required in response to the instant Office action.

Withdrawn - Objections to the Specification

6. Previous objection to the title for not adequately describing the claimed subject matter is withdrawn by virtue of Applicants' amendment.

7. Previous objection to the Abstract for containing an abbreviation, "CLF", without definition, is withdrawn by virtue of Applicants' amendment to the Abstract.

8. Previous objection to the specification for informalities concerning the brief description of the drawings is withdrawn by virtue of Applicants' amendment.

9. Previous objection to the amendment filed April 15, 2002 (Paper No. 9) under 35 U.S.C. § 132 is withdrawn with respect to Claim 26 by virtue of Applicants' amendment.

Maintained - Objections to the Specification

10. Previous objection to the specification for informalities on pages 35, 45, 51, and 56, concerning stray marks on the chemical structure is maintained. Applicants have requested that the amendment to correct this defect be held in abeyance. Since the instant Office action is non-final, such a request will be honored. However, a complete response to the instant Office action must include an amendment to correct this defect in the specification.

11. Previous objection to the amendment filed April 15, 2002 (Paper No. 9) under 35 U.S.C. § 132 is maintained with respect to Claim 38 by virtue of Applicants' amendment. Applicants' arguments are addressed below under sections concerning 35 U.S.C. § 112, first paragraph.

Withdrawn - Claim Objections

12. Previous objection to Claims 17-30 because of the informalities is withdrawn by virtue of Applicants' amendment.

13. Previous objection to Claim 20 under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim is withdrawn by virtue of Applicants' argument. Applicants note that KSQ-AT-ACP loading domains have an AT domain without an arginine at its active site while AT-ACP loading domains have an AT domain with an arginine at its active site.

Withdrawn - Claim Rejections - 35 U.S.C. § 112

14. Previous rejection of Claims 17-30 under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase "the target polyketide" is withdrawn by virtue of Applicants' amendment.

15. Previous rejection of Claims 17-30 under 35 U.S.C. § 112, second paragraph, as being indefinite for the parentheses of "(unsubstituted)" is withdrawn by virtue of Applicants' amendment.

16. Previous rejection of Claim 18 under 35 U.S.C. § 112, second paragraph, as being indefinite for the abbreviation "KS" is withdrawn by virtue of Applicants' amendment.

17. Previous rejection of Claims 19, 39, and 40 under 35 U.S.C. § 112, second paragraph, as being indefinite for the abbreviation "CLF" is withdrawn by virtue of Applicants' amendment.

18. Previous rejection of Claims 22, 29, 39, and 40 under 35 U.S.C. § 112, second paragraph, as being indefinite for the abbreviations "KSq" and "ATq" is withdrawn by virtue of Applicants' amendment.

19. Previous rejection of Claim 38 under 35 U.S.C. § 112, second paragraph, as being indefinite for the abbreviation "PKS" is withdrawn by virtue of Applicants' amendment.

20. Previous rejection of Claim 26 under 35 U.S.C. § 112, first paragraph, new matter, is withdrawn by virtue of Applicants' amendment removing the new matter from the claim; proper support for this amendment is found on page 27, lines 9-10, of the specification as originally filed.

21. Previous rejection of Claims 17-30 and 38-40 under 35 U.S.C. § 112, first paragraph, written description, is withdrawn by virtue of the Examiner's reconsideration. The withdrawal of the rejection is based on the fact that the art of polyketide synthases has developed to such an extent, with numerous examples of strikingly similar structure and function, that one of skill in the art, while not being able to predict the exact structure (sequence) of a particular PKS, does have enough general knowledge of PKS structure and function to utilize PKS enzymes as a generic genus.

22. Previous rejection of Claims 17-30 and 38-40 under 35 U.S.C. § 112, first paragraph, scope of enablement, is withdrawn by virtue of the Examiner's reconsideration. The withdrawal of the rejection is based on the fact that the art of polyketide synthases has developed to such an extent, with numerous examples of strikingly similar structure and function, that one of skill in

the art, while not being able to predict the exact structure (sequence) of a particular PKS, does have enough general knowledge of PKS structure and function to utilize PKS enzymes as a generic genus.

Maintained - Claim Rejections - 35 U.S.C. § 112

23. Previous rejection of Claim 38 under 35 U.S.C. § 112, first paragraph, new matter, is maintained. Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. At issue is the inclusion of a proviso which carves out the prior art noted in the specification from the scope of the claimed invention wherein the prior art is merely described (not used in a negation statement) in the specification as originally filed. Applicants rely on *In re* Johnson (and Farnham) 194 USPQ 187 (1977) and *In re* Driscoll 195 USPQ 434 (1977) as examples of the insertion of narrowing amendments to avoid the claims reading on the prior art. In both cases, Appellants were seeking support in their priority document for a subgenus disclosed in their instant application, which subgenus was a member of a larger genus disclosed in the priority document (the species was not disclosed in the priority document). This is distinct from the instant situation where Applicants are seeking to limit the scope of the claimed subject matter by virtue of a mere description of the prior art. The rejection is maintained because no where in the specification as originally filed is the art described on pages 12-13 used in a negation statement, describing Applicants' invention as this entire genus with the exception of the embodiment in the art that reads on it. Applicants also mention that Kuhstoss *et al.* did not fully appreciate the function of the Ks^Q domain and actually teach away from the true role of the Ks^Q domain. While all these may be true, the issue is whether or not Kuhstoss *et al.* teach a species within the genus claimed. The motivation of Kuhstoss *et al.* could be considered

an issue is used in a rejection under 35 U.S.C. § 103(a); that is not the case in the instant Office action.

Withdrawn - Claim Rejections - 35 U.S.C. § 102

24. Previous rejection of Claims 17, 18, 20-22, 24, 28, 29 and 30 under 35 U.S.C. § 102(b) as being anticipated by Kuhstoss *et al.* is withdrawn by virtue of Applicants' amendment to Claim 17 which adds a proviso that the hybrid PKS not be $Load_{tylosin}$-$Extender_{sprimycin}$. The Examiner notes, however, that this proviso is considered new matter. Therefore, the previous rejection is reiterated below since it would have been maintained in the absence of the new matter.

> "Claims 17, 18, 20-22, 24, 28, 29 and 30 are rejected under 35 U.S.C. § 102(b) as being anticipated by Kuhstoss *et al.* The instant claims are drawn to a polyketide synthase (PKS) that is a hybrid of a loading module and extension modules from different sources.
>
> Kuhstoss *et al.* teach a hybrid polyketide synthase (PKS) comprised of the loading module (KS^Q-AT-ACP) of the tylosin PKS and the extension modules of spiramycin PKS (see page 233, left column and Figure 3). The loading module of the tylosin PKS **inherently** has the capacity for decarboxylation as itemized in Claim 17. Said tylosin loading and spiramycin extension modules are not naturally associated with each other. The hybrid PKS produces a 16-membered polyketide (see Figure 3), which production attests to the ability of the loading domain to supply the extension modules with the growing polyketide chain. The loading module of the tylosin PKS contains a KS^Q domain (a ketosynthase domain having a glutamine, not a cysteine, as an active site residue) and the AT domain contains an arginine. The loading module of the tylosin PKS is specific for methylmalonyl-CoA and propionate and includes and acyl carrier protein."

Maintained - Claim Rejections - 35 U.S.C. § 103

25. Previous rejection of Claims 19, 23, 25, and 38-40 under 35 U.S.C. § 103(a) as being unpatentable over Khosla *et al.* (USPN 5,712,146) in view of Khosla (Chemical Reviews (1997) 97:2577-2590) is maintained. Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons.

Applicants argue that Khosla *et al.* did not appreciate the "existence of loading modules" and the instant invention requires such appreciation. The Examiner disagrees that the claimed invention requires such an appreciation. Khosla *et al.* clearly appreciated the modularity of polyketide synthases and the ability to produce hybrids. Said hybrids render obvious the instant claims as noted in the previous rejection.

Applicants argue that the discussion of type I/type II hybrids in Khosla *et al.* does not render obvious using a CLF domain because it is merely in the "definitions" section. The Examiner fails to see the relevance of the placement of the statement. Clearly, Khosla *et al.* envision all hybrids and define all domains of type I and type II PKSs. In this vane, the CLR version of the hybrid PKS is obviated. The significance of the CLF domain need not be emphasized, or even mentioned, by Khosla *et al.* when all combinations of domains, be it type I, type II or hybrids thereof, are envisioned.

Applicants argue that the approach of Khosla *et al.* is random and, due to the lack of appreciation for the significance of the CLF and/or loading domains, cannot obviate the claims. The Examiner disagrees. Regardless of the approach, Khosla *et al.* describe hybrid PKS systems. As such, Khosla *et al.* renders obvious the instant claims because the decarboxylating functionality is inherent in the molecules (sequences or domains or modules) taught by Khosla *et al.* The instant claims are drawn to products, and these products ARE rendered obvious by the disclosure of Khosla *et al.* Applicants argue that their "precise and tailored" approach goes beyond Khosla *et al.* While this may be true, the **approach** is not being considered for patentability herein – the products are.

Applicants argue that the approach disclosed by Khosla *et al.* does not produce hybrid PKSs apart from pure type II PKSs. The Examiner notes that Khosla *et al.* only make hybrid type II PKSs (ergo, no art rejection under 35 U.S.C. § 102); however, Khosla *et al.* do conceive of the invention claimed in the instant claims as noted above.

The rejection is reiterated below for completeness of the instant record:

> "Claims 19, 23, 25, and 38-40 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Khosla *et al.* (USPN 5,712,146) in view of Khosla (Harnessing the Biosynthetic Potential of Modular Polyketide Synthases. Chemical Reviews (1997) 97:2577-2590). The instant claims are drawn to hybrid PKS enzymes and loading domains using loading domains containing CLF, $AT_{malonyl}$, and $AT_{ethylmalonyl}$ domains.
>
> Khosla *et al.* teach the basic construction of type I and type II PKS enzymes. For type I, the enzymes minimally contain a ketosynthase (KS) domain, an acyltransferase (AT) domain, and an acyl carrier protein (ACP) domain (see column 19, lines 12-20). For type II, the enzymes contain a KS and AT gene, a chain length factor (CLF) gene, and an ACP gene (see column 2, lines 23-30). Khosla *et al.* teach hybrid PKS enzymes using a combination of "enzymes, modules, active sites or portions thereof derived from aromatic, modular or fungal PKS gene clusters" (see column 10, lines 40-45). Thus, Khosla *et al.* teach the combination of any of these domains to produce a minimal PKS. Khosla *et al.* specifically teach hybrid PKS enzymes combining type I and type II genes (see column 9, lines 47-50), which would include a loading domain containing a CLF domain in a PKS enzyme. Khosla *et al.* specifically teach optional polyketide gene clusters such as spiramycin (see column 14, line 31), whose AT domains use malonyl-CoA and ethylmalonyl (see Khosla page 2581, left column). Khosla *et al.* teach no differentiation between loading module AT domains and other AT domains, thus mixing and matching of all domains is wholly described.
>
> It would have been obvious to one of ordinary skill in the art to use the teachings of Khosla *et al.* to produce the claimed inventions because Khosla *et al.* describe all possible combinations of genes, modules, domains, and portions thereof. One would have been motivated to produce such PKS enzymes because of the great therapeutic potential of novel polyketides that can be easily produced, in combinatorial fashion, using the system of mixing and matching described by Khosla *et al.* One would have had a reasonable expectation of success that such combination of genes, modules, domains, and portions thereof would render functional polyketides due to the extensive similarities among modular and aromatic PKS enzymes (see Khosla)."

NEW OBJECTIONS/REJECTIONS

Claim Objections

26. Claim 28 is objected to under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. In the art, all loading modules contain an acyl carrier protein; if this were not the case, the loaded starter unit could not be transferred to the extension modules. Correction/clarification is required.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

27. Claim 16 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Nowhere in Claim 16 is "type I" PKS mentioned although all the language is virtually identical to other claims in the instant application which specifically cite "type I" PKSs. Moreover, the "multienzyme" limitation implies type I as well as the loading and extension module terminology. However, in the absence of the term, "type I", it is unclear if the instant claim should read only of type I PKSs or not. Clarification is required. The Examiner suggests amending the preamble of Claim 16 to read like Claim 17.

28. Claim 16 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as

the invention. The term "substantially" in claim 16 is a relative term that renders the claim indefinite. The term "substantially" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

29. Claims 16-30 and 38 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "loading module" is unclear as to its exact nature. In the art, this term is defined as described in Claims 39 or 43; however, Claim 28 attempts to further limit Claim 17 by particularly requiring the inclusion of an ACP domain. With this in mind, clearly the definition in the art (as found in Claims 39 and 43) is not intended and the claims must be clarified as to the definition of "loading module".

30. Claims 19 and 39 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In both claims, the option of having a CLF domain or a ketosynthase β domain is offered; however, in the specification these are defined as identical domains with different names in the art. The claim is confusing with both names being included. The Examiner suggests using on the CLF name of the domain since it is more common in the art. It is clear from the specification that a ketosynthase β domain is also intended in the scope.

31. Claim 22 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as

the invention. The nature of the KS^Q-AT^Q pair is unclear due to the second wherein phrase which seems to place ("N-terminal ketosynthase-like domain"). The Examiner suggests replacing this wherein phrase with limitations about how the KS^Q-AT^Q pair was derived from the KS-AT of an extension module (i.e., the active site cysteine was changed to a glutamine). Such language would help clarify the claim.

32. Claim 29 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The antecedent basis of "the KSq domain" in Claim 29, line 1, is unclear when the claim depends from Claim 17, as amended. The Examiner suggests amending the dependency to be from Claim 18. Claim 29 will be examined as if this change has been made by Applicants.

33. Claim 30 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "variants of rifamycin, etc." is unclear as to its metes and bounds. Clarification is required so that one of skill in the art would be able to readily recognize the scope of the claimed invention.

34. Claims 38-40 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In Claim 38, the phrase "wherein at least part of the first extension module is heterologous to said loading module or at least a domain thereof" is unclear wherein

the "part" is unlimited. Similarly in Claim 39 with reference to "portion thereof"...from different sources". A small as a single amino acid is considered a part or portion of the first extension module, and it is unclear how an amino acid can be heterologous (or not) to a loading module.

35. Claims 39, 40, and 43 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In Claim 39, the decarboxylating portion of the loading module is noted as "(decarbox)", but in Claim 43, this same portion is noted as "(dec)". Consistency in the claims is required.

36. Claims 39, 40, and 43 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "engineered domains" particularly in conjunction with "derived from different sources" is unclear since the following scenario could apply: PKS A and PKS B are from different sources; PKS A is engineered to PKS A' which looks like PKS B; a combination of PKS A' and PKS B is within the scope of the claimed invention but actually reads on simply PKS B alone. Clarification is required.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

37. Claims 17-30 are rejected under 35 U.S.C. § 112, first paragraph, new matter, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The phrase "with the proviso that the synthase is not composed of the loading module of the tylosin polyketide synthase coupled to the spiramycin polyketide synthase minus its natural loading module" is considered new matter as noted above in the maintaining the such a rejection against Claim 38.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

38. Claim 16 is rejected under 35 U.S.C. § 102(b) as being anticipated by Kuhstoss *et al.* The instant claim is drawn to a polyketide synthase (PKS) that is a hybrid of a loading module and extension modules from different sources.

Kuhstoss *et al.* teach a hybrid polyketide synthase (PKS) comprised of the loading module (KS^Q-AT-ACP) of the tylosin PKS and the extension modules of spiramycin PKS (see page 233, left column and Figure 3). The loading module of the tylosin PKS **inherently** has the capacity for decarboxylation as itemized in Claim 16. Said tylosin loading and spiramycin extension modules are not naturally associated with each other. The hybrid PKS produces a 16-

membered polyketide (see Figure 3), which production attests to the ability of the loading domain to supply the extension modules with the growing polyketide chain.

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

39. Claims 17, 18, 20-22, 24, 28-30, and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Khosla *et al.* (USPN 5,712,146) in view of Khosla (Harnessing the Biosynthetic Potential of Modular Polyketide Synthases. Chemical Reviews (1997) 97:2577-2590). The instant claims are drawn to hybrid PKS enzymes wherein the loading modules use naturally occurring $AT_{methylmalonyl}$ domains with an active site arginine, use an ACP, and use a KS^{Q} and make 16-membered macrolides. The instant claims are also drawn to loading modules wherein at least one domain is heterologous to the others.

Khosla *et al.* teach the basic construction of type I and type II PKS enzymes. For type I, the enzymes minimally contain a ketosynthase (KS) domain, an acyltransferase (AT) domain, and an acyl carrier protein (ACP) domain (see column 19, lines 12-20). For type II, the enzymes contain a KS and AT gene, a chain length factor (CLF) gene, and an ACP gene (see column 2, lines 23-30). Khosla *et al.* teach hybrid PKS enzymes using a combination of "enzymes, modules, active sites or portions thereof derived from aromatic, modular or fungal PKS gene

clusters" (see column 10, lines 40-45). Thus, Khosla *et al.* teach the combination of any of these domains to produce a minimal PKS. Khosla *et al.* specifically teach optional polyketide gene clusters such as spiramycin (see column 14, line 31), whose loading module naturally contains a KS^Q domain and whose AT domains naturally use malonyl-CoA and ethylmalonyl (see Khosla page 2581, left column). The Examiner notes that a naturally occurring KS^Q domain and one generated from an extension module KS domain (by mutating the active site cysteine to glutamine) have not been distinguished in the specification. Khosla *et al.* teach no differentiation between loading module AT domains and other AT domains, thus mixing and matching of all domains is wholly described.

It would have been obvious to one of ordinary skill in the art to use the teachings of Khosla *et al.* to produce the claimed inventions because Khosla *et al.* describe all possible combinations of genes, modules, domains, and portions thereof. One would have been motivated to produce such PKS enzymes because of the great therapeutic potential of novel polyketides that can be easily produced, in combinatorial fashion, using the system of mixing and matching described by Khosla *et al.* One would have had a reasonable expectation of success that such combination of genes, modules, domains, and portions thereof would render functional polyketides due to the extensive similarities among modular and aromatic PKS enzymes (see Khosla).

Summary of Pending Issues

40. The following is a summary of the issues pending in the instant application; each issue must be addressed in a complete response to the instant Office action:

a) The drawings are considered informal.
b) The application does not fully comply with the sequence rules.
c) The specification stands objected to for informalities on pages 35, 45, 51, and 56, concerning stray marks on the chemical structure.
d) Claim 28 stands objected to under 37 C.F.R. § 1.75(c), as being of improper dependent form.
e) Claim 16 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite, for omitting a reference to type I PKSs and for the term "substantially".
f) Claims 16-30 and 38 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the term "loading module".
g) Claims 19 and 39 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the option of having a CLF domain or a ketosynthase β domain that is confusing.
h) Claim 22 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the nature of the KS^{Q}-AT^{Q} pair.
i) Claim 29 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the antecedent basis of "the KSq domain".
j) Claim 30 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the term "variants of rifamycin, etc.".
k) Claims 38-40 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase "wherein at least part of the first extension module is heterologous to said loading module or at least a domain thereof".
l) Claims 39, 40, and 43 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for inconsistent language.
m) Claims 39, 40, and 43 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the term "engineered domains".
n) Claims 17-30 and 38 are rejected under 35 U.S.C. § 112, first paragraph, new matter.
o) Claim 16 stands rejected under 35 U.S.C. § 102(b) as being anticipated by Kuhstoss *et al.*
p) Claims 17-25, 28-30, 38-40, and 43 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Khosla *et al.* (USPN 5,712,146) in view of Khosla (Chemical Reviews (1997) 97:2577-2590).

Allowable Subject Matter

41. The Examiner notes that Claims 26 and 27 are considered free of the prior art. These claims are drawn to specific species of the genus of hybrid PKSs claimed in Claim 17. Claim 26 requires the AT of module 6 of the niddamycin PKS, and Claim 27 requires the AT of module 4 of the FK506 PKS. Such exact combinations in the hybrid PKSs cannot specifically be rendered obvious by Khosla *et al.* (USPN 5,712,146).

The Examiner also notes that the closest prior art is Marsden *et al.* who teach the combination of the loading module of the avermectin PKS and the extension modules of the erythromycin PKS. The hybrid PKS of Marsden *et al.* produces a 14-membered macrolide, such as in the "proviso" statement in Claims 16, 17, and 38.

Conclusion

42. No claims are allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (703) 305-1229. The examiner can normally be reached on Monday through Friday, from 8:30am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

KMK April 1, 2003